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Division of
Dockets Management (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0022
Request for Comments on: International Conference on Harmonisation; Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals.

Eli Lilly and Company (Lilly), as a global research based pharmaceutical company, is committed to the development of innovative medications for the treatment of important human diseases. Lilly welcomes the opportunity to comment on the ICH S8 draft Guidance.
Lilly participated indirectly in the ICH S8 process as a member of the HESI/ILSI Immunotoxicology Technical Committee. This committee had a representative on the ICH committee (Thomas Kawabata, Pfizer) through which the group communicated its concerns and questions. The ILSI Immunotox Technical Committee supported the goal to change the international (CMPMP) guidance from an 'all drugs' scenario to a 'for concern' approach for immunotoxicity testing. The latter position was adopted in the draft ICH S8 guidance. Lilly offers the following comments for your consideration.

HARMONIZED GUIDELINE ON NONCLINICAL ASSESSMENT FOR UNINTENDED IMMUNOSUPPRESSION (ICH S8)

GENERAL COMMENTS

We strongly agree with the general message of the guidance that evidence of immunotoxicity characterized as immunosuppression can usually be observed in standard nonclinical toxicology studies and that all compounds should not needlessly be screened for potential immunotoxicity using immune function assays without cause. We furthermore agree that follow-up studies may be necessary to define potential mechanisms.

We would suggest that consideration be given to including biotechnology compounds in this guidance. It would provide a more thorough guideline to companies developing these products. We feel it can be easily incorporated because the immunotoxicity concern for an immunomodulatory biotechnology compound should be the same as for an immunomodulatory small molecular weight compound.

2005D-0022 C1

In general, we believe that this guidance is lacking published references that support the statements presented and would urge that references be included. This would be particularly helpful in Appendix 1. For example, we think that inclusion of the Society of Toxicologic Pathology document authored by Haley et al. entitled "Best Practice Guideline for the Routine Pathology Evaluation of the Immune System," would strengthen section 1.3 Histopathologic Examination in Appendix 1's Methods to Evaluate Immunotoxicity.

Lastly, we would urge that while conducting "the weight of evidence review" to determine the need for additional nonclinical immunotoxicity assessment, clinical physicians be included in the discussions. We believe that earlier collaboration between nonclinical and clinical professionals provides an opportunity for better interpretation of the immunotoxicity risk assessment to humans and allows the inclusion of biomarkers of potential immunotoxicity earlier in clinical trials if warranted.

SPECIFIC COMMENTS

Section 1.2 Background

Lines 82-89 discuss the value of performing immune function studies on anti-proliferative compounds. For clarity, please add "antiproliferative" to precede "drug-risk assessment" in Line 86.

Section 1.3 Scope of the Guideline

Line103: We suggest that biologic compounds be included in this guidance as discussed above.

Section 2.1. Assessment of Potential Immunotoxicity

Line130: Remove the second "the" in the sentence so it will now read "The initial screen for potential immunotoxicity involves standard toxicity studies."

Section 2.1.1 Standard Toxicity Studies

Line146: Sentence should be ended by a ":" instead of a period.

Line 165: Replace the word 'and' with 'or' since statistical significance does not necessarily equal biological significance or adversity.

Section 2.2.1 Selection of Assays

Line217: The first sentence of this paragraph appears out of place. Perhaps it should be deleted and begin the paragraph with the next sentence "Where a specific target is not identified, ..."

Section 4. Timing of Immunotoxicity Testing in Relation to Clinical Studies

Line 260: We believe an important distinction should be made to clarify that the "large patient population exposure" is defined as a multi-dose study. Furthermore, it would be helpful if guidance could be provided on whether this means Phase II, Phase III or Phase IV development. If truly the intent is to allow for incorporation of appropriate immunotoxicology endpoints in clinical studies, then one might infer that the intent is to perform nonclinical immunotoxicity assessments concurrent with or prior to Phase II.

Line 266: We believe a stronger statement is necessary with regard to the timing of testing in immunosuppressed patients. Please replace the word "can" in Line 266 with the word "should".

Appendix 1, Section 1.1 Hematology and Clinical Chemistry

Line 285: remove the word "for" in the first sentence, to now become "...are recommended to assess immunotoxicity."

Line 296: Although thorough bleed out prior to necropsy is good practice for dogs, the primate spleen does not contract significantly; therefore, bleed out is only important for dogs.

Appendix 1, Section 1.2 Gross Pathology and Organ Weights
Line 293: To remain consistent with the STP Best Practice Guideline for the Routine Pathology Evaluation of the Immune System document, we would also suggest adding the following to the end of the first sentence: "and any gross lesions of a lymphoid organ should also be collected for microscopic evaluation."

Appendix 1, Section 1.3 Histopathologic Examination
Line 313: This guidance should refer the reader to the STP Best Practice document for further information regarding use of a unified terminology description for histopathologic evaluation. Three primary points are emphasized in the evaluation: 1) each lymphoid organ has separate compartments that support specific immune functions, 2) these compartments can and should be evaluated individually for changes, and 3) descriptive, rather than interpretative terminology, should be used to characterize changes within these compartments. In order to achieve an accurate, consistent and useful "semi-quantitative description" it is necessary to develop consensus on terminology used in characterization of lymphoid tissue changes. Whenever possible, semi-quantitative/descriptive terms (i.e. reduced numbers of lymphocytes) rather than interpretative terms (i.e. lymphoid atrophy) for registering lymphoid tissue abnormalities is recommended. To illustrate this point further, consider potential stress-induced changes of the thymus; a semi-quantitative description such as: "thymus, cortex, decreased lymphocytes, marked" would be preferable to "thymic involution".

Appendix 1, Section 1.4 Interpretation of Stress Related Changes
Lines 316-326: There is the perception, which is reflected in this section, that stress-related changes in immune parameters observed in toxicology studies should automatically be dismissed. In contrast, we believe significant effects on immune parameters should be reported (regardless of the mechanism). Without benefit of mechanistic studies, it becomes a judgment call made without proof that the stress response (defined as neuroendocrine-immune effects) is not drug-related or will be absent in humans. The reporting of significant changes in immune parameters may also help alert clinicians to the immunomodulatory properties of therapeutic drugs that may have otherwise been overlooked. Additional support for limiting the stress exclusion is discussed below.

In standard toxicity screening, doses sufficient to produce overt toxicity and significant body weight loss (such as maximum-tolerated-dose levels) are expected to induce a stress response with associated increase in corticosterone levels (Pruett, et al., 1993; Pruett 2001). However, as pointed out by the same authors, there is less evidence regarding a stress effect on the immune system at lower doses of toxicity and only in cases where a drug substantially elevates glucocorticoid levels, should the possibility of immunosuppression by this mechanism be considered. There is also recent evidence that animals can accommodate to chemical-related increases in serum corticosterone over time and that Sprague-Dawley rats (a strain frequently used in toxicology studies) are relatively insensitive to ethanol induced corticosterone effects. Additionally, these animals actually accommodated to the corticosterone release over 30 days but still presented with reduced thymus weights and depressed immune function (Hebert et al., 2005).

Routinely ascribing changes in immune parameters as stress related in standard toxicology studies has led to the general misconception that any weight loss will indirectly affect immune parameters such as thymus weight. In fact, very significant weight loss must occur before most immune parameters are affected. For example, in a 2-week food restriction study in Sprague-Dawley rats, immune cell changes were manifested only after the degree of weight loss reached moderate to severe levels defined as terminal body weights reduced 40-60% of control (Levin et al., 1993). WBC counts were the least sensitive to body weight loss with bone marrow cellularity being the most sensitive.

Decreased thymus and liver weights occurred only in animals with body weight loss greater than 30%. Further evidence that the immune system is relatively insensitive to weight loss per se is supported by several studies (Sharer, 1977; Oishi et al, 1979; Pickering and Pickering 1984, Ogawa et al., 1985).

Relative to thymus weight decreases and stress, it is recognized that not all chemically induced reductions in thymus weights leads to immunotoxicity in the test species (Comment et al., 1992). However, because this can only be determined by functional testing of the immune response, decreases in thymus weights provide a sensitive first tier indicator, or biomarker, of potential consequences of chemical or drug treatment on the immune system and therefore should not be ignored.

Therefore we agree with the statement that the evidence of stress should be compelling and recommend defining this effect by increases in either adrenal weights or serum corticosterone levels, or due to overt toxicity. If stress-related effects on immune parameters at doses other than the MTD are diagnosed in a standard toxicology study, they should be reported (regardless of whether it is a direct or indirect mechanism) because the overall effect is potentially detrimental to immune responsiveness and should be identified. The only advantage to understanding the mechanism is if it is believed that humans treated with the drug will not have the same stress response, however, proving this is beyond the current scope of routine toxicity screening studies.

Appendix 1, Section 2.3 Immunophenotyping
Lines 379-385: This section appears to be out of place here and may confuse the reader. If the intent is to present that immunohistochemistry is an alternative to flow cytometry but has limitations, it should be worded as such and a conclusion drawn as to when it is appropriate to use either technology platform.

Appendix 1, Section 2.4 Natural Killer Cell Activity Assays
Line 402: Change the word "assay" to "assays".

Appendix 1, Section 2.5 Host Resistance Studies
Line 425: Change the first word "assay" to "assays".

Appendix 1, Section 2.7 Assays to Measure Cell-Mediated Immunity
Line 448: Change the word "cells" to "cell".

References:

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Haley, P.J., et al. (2005). Best practice guideline for the routine pathology evaluation of the immune system. *Toxicol. Pathol* (in press).

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Pruett, S.B., Ensley, D.K. and Crittenden, P.L. (1993). The role of chemical-induced stress responses in immunosuppression: A review of quantitative associations and cause-effect relationships between chemical-induced stress responses and immunosuppression. *J. Toxicol. Environ. Hlth.* **39**: 163-192.

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Ogawa, Y., Matsumuoto, K., Kamata, E., Ikeda, Y. and Kaneko, T. (1985). Effect of feed restriction on peripheral blood and bone marrow cell counts of Wistar Rats. *Exp. Anim.* **34:** 407-416.

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Sincerely,

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